REMARKS

Claims 19, 20, 25-27, 29, 32, 33, 35, 36, 38-40, 42, 43, 45-47, 49, 50, and 52-61 are pending in this application.

Priority

This application claims priority to Application Nos. PCT/US00/22507; 60/183,356; 60/181,684; and 60/149,378. The outstanding Office Action acknowledges that "Applicants are entitled to priority to at least Application 60/181,684 and 60/183,356," but the Office Action is silent with respect to Applicant's earliest priority claim. Office Action of May 14, 2008, at 2. For the reasons set forth in previous replies, Applicants maintain that they are entitled to priority to Application No. 60/149,378, filed August 17, 1999.

Novelty

The Examiner has rejected claims 19, 20, 26, 27, 29, 39, 40, 42, 43, 45-47, 49, 50, and 52, 52-57, and 59-61 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Publication No. 2006/0067933 ("Gross et al."), which claims priority to Application No. 60/115,068 (filed January 7, 1999). The Examiner states that the '068 priority application discloses BCMA polypeptides, fusions of a BCMA protein to a heterologous protein, and compositions thereof. The Examiner acknowledges, however, that "[c]laims 32, 33, 35, 36, 38, and 58 are allowable over the art of record." Office Action of May 14, 2008, at 4.

Independent claims 46 and 60 relate to pharmaceutical compositions comprising a soluble BCMA polypeptide. The '068 application does not provide an enabling disclosure of a soluble BCMA polypeptide. BCMA is a membrane protein with a

transmembrane domain at approximately residues 53-81. "By their very nature, membrane proteins are insoluble in water." Goding, Immunology and Cell Biology 81: 497–498 (2003). The smallest fragment of BCMA contemplated by the '068 application is amino acids 1-150 of SEQ ID NO:6. Since this nearly full-length fragment retains the transmembrane domain, it remains an insoluble membrane protein. Thus, the '068 application does not provide an enabling disclosure of the subject matter of claims 46 and 60 and corresponding dependent claims.

By a similar rationale, the '068 application does not provide an enabling disclosure of the pharmaceutical compositions of independent claims 19 and 57. These claims recite BCMA polypeptides comprising an amino acid sequence that binds to BAFF and is at least 95% identical to amino acids 1-51, 8-41, or 1-52 of SEQ ID NO:1. The insoluble BCMA polypeptides disclosed by the '068 application would not bind BAFF. Moreover, the skilled artisan would not know how to use a pharmaceutical composition comprising an insoluble, inactive polypeptide. Thus, the '068 application does not provide an enabling disclosure of the subject matter of claims 19 and 57 and corresponding dependent claims.

Finally, independent claims 39 and 59 relate to pharmaceutical compositions comprising a polypeptide that comprises a BCMA polypeptide consisting essentially of an amino acid sequence that binds to BAFF and is at least 95% identical to amino acids 1-51, 8-41, or 1-52 of SEQ ID NO:1. The '068 application does not provide an enabling disclosure of such polypeptides. Again, the minimal BCMA fragment disclosed by the '068 application comprises amino acids 1-150. Thus, any BCMA polypeptide taught by

the reference is far longer than those recited in claims 39 and 59 and corresponding dependent claims.

Applicants respectfully submit that all of the pending claims are patentable over Gross et al. An allegedly anticipatory reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. Elan Pharm., Inc. v. Mayo Foundation for Medical and Education Research, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003). As discussed above, the disclosures of Gross et al.'s earliest priority document (Application No. 60/115,068) would not allow the skilled artisan to make and use the pharmaceutical compositions of the pending claims without undue experimentation. The next-earliest application to which Gross et al. claim priority is Application No. 60/169,890 (filed December 9, 1999). Even if Gross et al. are entitled to priority to the '890 application, which Applicants do not concede, the 102(e) date of U.S. Publication No. 2006/0067933 is later than Applicants' earliest priority date. The reference is not prior art.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and timely allowance of the claims. Applicants invite the Examiner to call the undersigned Applicants' representative with any questions or comments.

Please grant any additional extensions of time required to enter this response and charge any additional fees to deposit account 06-0916.

Respectfully submitted,

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Dated: September 17, 2008

By: _____

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ATTACHMENT

chemokines and chemokine receptors in an introductory chapter for the uninitiated. It would also have helped if the new terminology for chemokines were included in this book. Despite these minor shortcomings, in general, this is a good reference book for individuals who work in the general area of infectious diseases, cytokines and chemokines. It may also be a useful source of reading and general reference for students, active researchers and clinicians who are similarly interested in this area of research. The illustrations are generally good, however, some must have been copied from coloured originals as the reproductions are not clear.

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MEMBRANE PROTEIN PROTOCOLS

Edited by Barry S Selinksky. Humana Press, Totowa, New Jersey, USA, 2003. 334 pages. Price: US$100.00.

Methods books seem to come in two main categories. Some are written with a view to giving general principles and critical discussion of approaches to problems, illustrating the strengths, weaknesses and pitfalls with specific examples. This type of book is generally written by a single author or a small group of authors. Others, including this one, are more in the nature of a compendium of short chapters which are essentially protocols showing 'how we did it', and are generally written by a large number of different authors. There is a place for both types of books.

Membrane proteins are particularly difficult to work with. In higher organisms, they are complex glycoproteins which require a great deal of help from their friends, including chaperonins, signal peptidases, glycosyl transferases, glycosidases and other enzymes to achieve their mature and correctly folded state and to promote disulphide bond formation. Although something like half of all protein genes may encode membrane proteins, individual membrane proteins are generally of very low abundance, typically only one part in 10 000 of the total cellular protein.

By their very nature, membrane proteins are insoluble in water. Before they can be studied in isolation or purified, they have to be solubilized, most commonly by detergents which replace the planar lipid bilayer with a curved amphipathic micelle. Choice of the 'right' detergent is often critical, but tends to involve a mixture of empirical trial and error, intuition and just possibly a trace of logic.

Solubilization of a membrane protein in detergent is only the beginning of many difficulties, because many of the standard fractionation procedures cannot be applied owing to the necessity of the presence of detergent in the medium. If detergent is removed, the micelles bound to the protein will usually dissociate and the protein will precipitate or stick to the sides of the tube. The presence of detergents also greatly complicates the crystallization of membrane proteins.

For proteins which only cross the membrane once, it is often possible to solubilize the extracellular domain by carefully controlled proteolysis, converting it into a water-soluble protein that can be handled in the same way as any other water-soluble protein. Of course, this approach leaves behind the very interesting and important transmembrane region, and cannot be used for pumps and channels, which cross the membrane many times.

The combination of insolubility and low abundance makes the purification and crystallization of membrane proteins a major challenge. In spite of these difficulties, there has been very substantial progress. Many of the key advances are described in this book.

Structural studies involving crystallization require large amounts of protein. The problem of low abundance can be tackled in at least two ways. First, you can choose an organism such as *Halobacterium halobium*, in which the relevant protein (in this case, bacteriorhodopsin) is present in unusually large amounts. This is only possible in special cases. A more common strategy is to clone the gene or cDNA and express it in as high amounts as possible in a heterologous system. Extensive experimentation with regard to the choice of promoters and other regulatory elements and host cells is usually required.

Unfortunately, the ubiquitous *Escherichia coli* is not very well suited to expression of heterologous membrane proteins from higher organisms because it lacks much of the necessary machinery for post-translational processing. Membrane proteins from eukaryotic cells generally require expression in eukaryotic cells, although it may prove helpful to transfer mammalian cells into yeast or insect cells. The first section of the book consists of seven chapters in which the use of heterologous expression systems is explored. The first three chapters show that in spite of difficulties, bacterial expression may sometimes be rewarding.

The second section consists of only three chapters, and deals with the strategic choice of detergents for solubilization of membrane proteins. In view of the importance of this topic, it would have been helpful to have a few more examples. The third section, which is the longest, consists of 12 chapters on purification of a variety of membrane proteins. The final section is devoted to structural analysis of membrane proteins, but has only two chapters, one on crystallization of bacteriorhodopsin in lipidic cubic phases, and the other on the use of the optical biosensor.

This book consists of a series of recipes, which may or may not be useful for your own favourite protein. Its weakness is the paucity of discussion of general guiding principles. I find books of this type frustrating because whatever generalizations are possible are either not made at all, or are difficult to locate. But if you are trying to express, solubilize, purify or crystallise a membrane protein, browsing in this book may give you some ideas of things to try. It is not a book to be read from cover to cover, but rather to be dipped into in the hope that someone has encountered a similar problem, and just possibly might offer a solution.

The usefulness of methods books is that they provide more detail concerning experimental procedures than can be covered in the journals, but they cannot be a substitute for keeping up

with the current literature. Indeed, one of the great difficulties in editing a book of this kind is the inevitable lag between writing and publication. Most references are from the mid 1990s, and few are as late as 2000. In the meantime, there has been very substantial progress in the purification and crystallization of the most recalcitrant membrane proteins, those with multiple transmembrane domains such as pumps and channels.

Spectacular success has recently come out of MacKinnon's laboratory at the Rockefeller University, where novel strategies, including judicious choice of organism, have allowed the structure of a voltage-dependent potassium channel to be determined at high resolution. At last, we can see a plausible mechanism of how it works. Unfortunately, this advance came too late for inclusion in this book. Such is the march of science.

If there is to be a second edition of this book, comparison with the current one would reveal that the pace is quickening for this class of difficult but fascinating and important proteins. We might expect a new edition to include greatly increased coverage of successful determination of the structure of pumps and channels. Methods for approaching the immense technical difficulties are becoming more reliable and feasible. At long last, we are beginning to see how membrane proteins work at the atomic level. There is a growing sense of satisfaction from the improved understanding of normal physiology. In the longer term, this should lead to more effective treatment of disease.

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PRACTICAL IMMUNOLOGY

Frank C Hay and Olwyn MR Westwood. Blackwell Science, Oxford, UK, 2002. 400 pages. Price A$135.30

This is the fourth edition of Practical Immunology. The first edition from 1976 graces my laboratory shelf and has been used over the years by students and research assistants. The current edition has the same audience in mind. So often the basic principles behind techniques are assumed, but here is a text that provides this information. I have no doubt that this book will still be useful in the laboratory despite the trend to search for everything on the Web. The authors have set up a website to maintain updates to methods and to be a forum for comments from readers, although at the time of writing this review this site was not accessible.

This book contains 11 chapters covering a comprehensive range of immunological techniques. The first five chapters are devoted to antibodies, their isolation and characterization, monoclonal antibodies, antigen–antibody interactions, the use of antibodies as probes, and immunoassays. The next five chapters deal with cells, their isolation, culture techniques, measurement of effector functions and bioassays for cytokines. The last chapter deals with immunological studies *in vivo*. There are also three appendices: 'Buffers and media', 'Basic techniques and useful data', and 'Equipment and manufacturers index'.

The format of the book makes it easy to read. Each section begins with a short paragraph introducing the method. This is followed by a list of the 'Materials and equipment' required, and then the 'Method' which is highlighted in a box, and this is followed by a section on 'Technical notes'. Each chapter concludes with a list of articles entitled 'Further reading'.

I think overall the book meets its objective. There are instances where I thought a procedure was rather dated and unlikely to be used, such as the use of defibrinated blood for lymphocyte isolation. There are other instances where more recent and commonly used procedures were not included, such as the use of cell surface biotinylation rather than radioiodination for immunoprecipitation analysis. There have also been tremendous advances in the use of fluorescent probes for labelling lymphocytes for tracking cells *in vivo* and for analysing cell division and these methods were not mentioned in the text. There was no mention of MHC tetramers to determine the frequency of antigen responsive cells *in vivo*, or of procedures for intracellular cytokine staining. One frustrating aspect was the inadequate cross-referencing to other sections of the book, so looking for a supplementary procedure was often not easy. In some cases, the arrangement seemed strange. Cell counting using a haemacytometer would seem more appropriate in the appendix on 'Basic techniques and useful data', than in chapter 11. The 'Further reading' sections at the end of each chapter would be more useful if the articles listed were referred to in the body of the chapter which, in most cases, they were not. Perhaps there could have been concluding sections of the chapters that would lead the reader to want to look through this reference list to find other procedures that were not discussed. An important exclusion from the text was references to information on chemical safety. Websites for radioisotope health and safety were listed in several places in the text, but websites to alert the reader about chemical safety for toxic reagents were not included. Such information could have been included with the list of useful websites at the end of Appendix B.

In conclusion, despite the trend to search for information on the web, I think this book has a place in the laboratory. This book provides important basic information on immunological techniques which is a must for students and research assistants. Even for the more experienced, this book is an easy reference for a buffer or media formulation, or a reminder of a technique that has not been used for a while. The book, however, would certainly have extra value if it was accompanied by a CD.

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